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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER

BORIN, MICHAEL L

ART UNIT PAPER NUMBER

1631

DATE MAILED: 02/24/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/753,869

Applicant(s)

GRIFFEY ET AL.

Examiner

Michael Borin

Art Unit

1631

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 24 November 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 12 and 27-29 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 12 and 27-29 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____

DETAILED ACTION

1. Appeal Brief filed 11/24/2004 is acknowledged.

Upon further consideration of the issues in the case, several new grounds of rejection were deemed necessary. The finality of previous Office action is withdrawn. The following rejections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claims 27-29 are added. Claims 12, 27-29 are pending.

Claim Rejections - 35 USC § 102

2. Claims 12, 28, 29 are rejected under 35 U.S.C. 102(e) as anticipated by Horlbeck (1999) US Pat. No. 5,880,972.

The instant claims are drawn to method of identifying *in silico* compounds of a virtual library comprising steps of:

- a) dissecting a compound into fragments,
- b) adding fragments in sequential synthesis rounds,
- c) tracking the addition of the fragments.

Horlbeck teaches a method and apparatus for the generation and representation of chemical libraries (e.g. see col. 8, lines 39-42 "to provide a combinatorial chemical library ... without performing synthesis") including "non-

polymeric small molecules" within the scope of the presently claimed invention (see col. 9, lines 10-20; Figures and Examples). The reference teaches that when a compound generated using combinatorial chemistry is found to have a desirable property, it is important to be able to determine the manner in which it was synthesized so that it can be made in large quantities. A scheme therefore is needed by which the reaction history of small molecules generated using combinatorial chemistry could be tracked (see col. 2). Virtual synthons (including starting materials and reagents) are entered into a database (e.g. see col. 7, lines 1-5 and fig. 6). Synthons, being reactants that will add molecular fragments to other synthons, read on the presently claimed fragments and corresponding reagents. The synthons can be selected by various criteria (see col. 12, bottom through col. 13), one of which is reaction history (Fig. 2C), i.e., the ease of synthesis of the compound from fragments. The synthons are linked to one another *in silico* to form virtual libraries of molecules (e.g. see col. 13, lines 47-67; col. 14, lines 17-23). Using synthesis instructions generated *in silico and tracking of library* molecules (e.g. see examples; patent claims e.g. claim 1 method steps a-d), library members are synthesized (e.g. linked) and screened (e.g. see col. 14, lines 59-65: and col. 13, lines 57-60: "Using techniques and criteria such as those described, a proposed library **608** is automatically generated by the expert system **603**. This library can be represented as a set of synthons for stage 1 and synthons for stages 2-N"; see fig. 6 and **619** "Make and Screen the Library"). The reference proposed

library of compounds is a virtual library, a subset of which is ultimately synthesized (e.g. see **613** in figure 6), preferably robotically, as illustrated by the Horlbeck reference incorporation of the automated syntheses methods of Agrafiotis et al. '972 (e.g. col. 7, lines 1-23). Agrafiotis et al. '972 teaches the use of computer generated synthesis instructions for automated synthesis of library members.

3. Claims 12, 28, 29 are rejected under 35 U.S.C. 102(e) as anticipated by Agrafiotis et al. US Pat. No. 5,684,711.

Agrafiotis teaches the use of a Synthesis Protocol generator that generates synthesis instructions. The (e.g. individually preprogrammed) instructions identify which reagents from a reagent repository are to be used and the manner in which they are mixed, and under what conditions (e.g. see col. 13, lines 55-65). The reference includes an example in which libraries of thrombin inhibitors (e.g. "non-polymeric small molecules" within the scope of the presently claimed invention) related to the molecule D-Phe-Pro-Arg are synthesized. One library is composed of Y-Pro-Z where Y is one of ten D-Phe substituents and Z is one of 100-150 commercially available primary amines from a reagent repository. Y and Z correspond to the fragments in the current claim. The fragments are selected in silico and the syntheses (linking of fragments) are also performed in silico. The library is then synthesized by a Chemical Synthesis Robot using the synthesis protocols generated by a Synthesis Protocol Generator (e.g. see col. 22, lines 12-

31). This anticipates every step of the claimed invention. The comprising language in col. 24, lines 41-53 and col. 25, lines 36-56 includes any means of synthesizing the compounds, including by automated synthesis.

Claim Rejections - 35 USC § 103

4. Claims 12, 27-29 are rejected under 35 U.S.C. 103(a) as obvious over Walters et al.

The instant claims are drawn to method of identifying *in silico* compounds of a virtual library comprising steps of:

- a) dissecting a compound into fragments,
- b) adding fragments in sequential synthesis rounds,
- c) tracking the addition of the fragments.

Walters et al reviews different strategies of virtual screening. One of the strategies, "chemically aware builder" comprises presenting components of the virtual library as combination of reagents and corresponding reactions. As such the method reads on the claimed method wherein a compound is defined by synthetic rounds between its chemical components. Further, the review describes another software, "Computer-Aided Estimation of Synthetic Accessibility", that evaluates members of the library by their synthesizability, i.e., by their building blocks and chemical reactions among them.

Although neither of the methods discussed above requires characterization of each compound of the library (as the instant method does), it would be *prima facie* obvious to one skilled in art to characterized any compound of interest, and thus to extend, if needed, such characterization to each compound of the library.

During the course of prosecution applicant argued that the "Chemically aware" builder does not present components of the virtual library as combinations of reagents and reactions, and has no basis on real world reactions. Examiner disagrees. The caption of Figure 1 addresses the method as examples of reactions. Further, the basis for the statement that Figure 1 is not based on "real world reactions" is unclear. Reactions depicted on the figure, e.g., of aldehydes and amines, or carbonylchlorides and amines, are trivial reactions well known to an organic chemist. The figure represents reagents that will readily interacting a "real world reactions".

Applicant further argued that in "Chemically aware builder" neither the compounds are dissected into fragments, nor there the fragments are added in synthetic rounds. However, every line in Figure 1 is seen by Examiner as representation of member of a compound library dissected into fragments and presented as a synthetic round leading to the target compound.

Further, applicant asserted that the CAESA software described in the reference uses "generalized synthetic transformations" whereas the claimed method "recites association with at least one reagent". Examiner does not see difference between these two highlighted definitions of "generalized synthetic transformations" and "association with at least one reagent". The former is the

same generic as the latter. Further applicant asserts that the CAESA software does not provide adding of constituent fragments. The software would have had no use, had it not been adding fragments and assessing synthetic rounds leading to the target compound.

Finally, applicant provided argument based on distinction between "identifying" and "characterizing". First, in regard to "insight into the meaning of the term identifying", this definition is not in the claim language, and it can not be because the claims can not be drawn to identifying a "one to one link" because they recite "at least one" (i.e., a plurality" of reagents. Further, the dictionary definition of the term "characterization" for some reasons emphasizes "a description of qualities or peculiarities" as applied to places of interest. Examiner finds the first meaning "an instant of characterizing" to be more fitting to the instant situation in which a compound is characterized (or identified) by its fragments and reactions therebetween. Further, other dictionaries offer similarly fitting definitions, e.g.,

"A special type of characterization translates an abstract property into a complete list of examples and models"

<http://mathworld.wolfram.com/Characterization.html>

or

"the application of techniques of examination by which characteristic properties of the constituent material of traded goods can be identified"

<http://www.webref.org/anthropology/c/characterization.htm>

5. Claim 27 is rejected under 35 U.S.C. 103(a) as) as being unpatentable over Horlbeck (US Pat. No. 5,880,972) as applied to claims 12,28,29 above, and further in view of the following. The reference does not specifically state that the

fragments should be selected based on their commercial availability. However, the reference states that those skilled in the relevant art will appreciate that many different rules can be incorporated into the knowledge base, and the scope of invention is not limited to fragments created by any particular rule. Those skilled in the relevant art will appreciate that many different techniques and criteria can be used to generate a representation of the library, and this aspect of the referenced invention is not limited to any one or more techniques or criteria. (see col. 12, bottom; col. 13, bottom). Therefore, it would be *prima facie* obvious to an artisan at the time the invention was made to select appropriate criteria for generating fragments, and one would be motivated to account for commercial availability of reagents, as it is desirable to be able to synthesize compound of interest from reagents that are commercially available.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

6. Claims 12,28,29 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-26 of copending Application No. 09/076214. Although the conflicting claims are not identical, they are not patentably distinct from each other because the patent application claims teach all of the presently claimed method limitations. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

7. Claim 12,28,29 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6 of copending Application No. 09/400,150. Although the conflicting claims are not identical, they are not patentably distinct from each other because the patent application claims teach preparing non-peptide compounds utilizing all of the of the presently claimed method limitations. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

8. Claims 12,28,29 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-18 of U.S.

Patent No. 6,253,168 (6/26/01). Although the conflicting claims are not identical, they are not patentably distinct from each other because the patent claims teach all of the presently claimed method limitations including ultimate syntheses (e.g. see patent claim 18) in which manual or automated syntheses would be immediately envisaged (e.g. anticipated) or alternatively obvious to one of skill in the art. The patent and the application are claiming common subject matter because "generating database comprising information about member compounds in a virtual library of compounds" (preamble in referenced claims) is the same as identifying compounds of *in silico* library by its fragments and transformations stored in database (as instantly claimed). The method steps are the same.

Examiner maintains that it would be obvious to an artisan that information obtained by generating the database information as claimed in the reference will serve as a descriptor and identifier of a target compound.

9. Claim 28 is provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable co-pending applications Nos. 09/076214, or 09/076214, in view of Horlbeck (US Pat. No. 5,880,972).

The co-pending applications are applied as stated above. Although the co-pending applications do not state that the fragments should be selected based on their commercial availability such consideration would be obvious to one skilled in

the art as explained in Holbeck et al. See rejection of claim 28 under USC103(a) above.

This is a provisional obviousness-type double patenting rejection.

10. Claim 28 is rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over of U.S. Patent No. 6,253,168 in view of Horlbeck (US Pat. No. 5,880,972).

U.S. Patent No. 6,253,168 is applied as stated above. Although the '168 patent does not state that the fragments should be selected based on their commercial availability such consideration would be obvious to one skilled in the art as explained in Holbeck et al. See rejection of claim 28 under USC 103(a) above.

Conclusion.

11. No claims are allowed

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Borin whose telephone number is (571) 272-0713. The examiner can normally be reached on 9am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel, Ph.D., can be reached on (571) 272-0718. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



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Art Unit 1631

mlb